Modern Concepts of Cardiovascular Disease

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SOME CLINICAL ASPECTS OF REFRACTORY HEART FAILURE

Shortness of breath and extra vascular accumulations of fluids in individuals with heart disease are so commonly due to non-cardiac illnesses that a diagnosis of heart failure should never be taken for granted. Once such a diagnosis is established, the physician should attempt to answer at least four questions: 1) what precipitated failure, 2) what associated diseased states are present, 3) what is the nature and extent of the cardiac disease, and 4) what treatment has been used. This multilateral approach is necessary for effective treatment and for evaluating prognosis. When an individual fails to respond to "optimal" treatment, he is said to have refractory or intractable heart failure. The term "optimal" treatment, however, is difficult to define.

The heart cannot be treated in vacuo. What is regarded as specific optimal treatment for the heart may not only not benefit the individual but under special circumstances may be harmful or even disastrous. For instance, failure to recognize precipitating factors, such as infections of the urinary tract, may not only render cardiac therapy ineffective but diuretics, which are otherwise indicated, may be dangerous.

Oral temperature is notoriously inaccurate in the dyspneic individual. A normal temperature does not exclude infection in the diabetic cardiac nor in an elderly debilitated cardiac patient. Indeed, muco-purulent sputum in any afebrile cardiac indicates infection and may require antibiotic therapy.

Unrecognized associated diseases such as thyrotoxicosis, myxedema, anemia, beri-beri, cirrhosis, prostatism or any obstructive uropathy, pericardial or pulmonary vascular disease may likewise interfere with restoration of cardiac compensation by specific cardiac therapy. Some of these diseases such as beri-beri or anemia may be the sole cause of heart failure and may respond only to non-cardiac specific medical therapy and others such as arterio-venous fistula or constrictive pericarditis only to specific surgery. Anti-diuretic drugs such as morphine, demerol, and codeine, which are so desperately needed for sedation or for cough may decrease or nullify in susceptible individuals the effect of diuretic drugs. Persistent refractory dyspnea may be due to pleural effusion, the physical signs of which are much more deceptive than equivalent amounts due to primary pulmonary disease. Perhaps this difference is due to the additive effect of the physical findings of the underlying lung disease. Allergy is as common in the cardiac as it is in the non-cardiac individual. Respiratory symptoms due to allergy will not respond to cardiac therapy. Many instances of so called cardiac asthma are bronchial asthma in individuals with cardiac disease.

For all these reasons, an individual presumably in refractory heart failure requires a thorough physical examination including roentgenograms of the chest. The entire therapy must be reviewed with respect to its adequacy, toxicity, and unavoidable side effects. No one can be a competent cardiovascular specialist without being a competent internist.

The direct treatment of congestive heart failure consists of 1) increasing cardiac efficiency and 2) decreasing cardiac load. In rare instances, one of these two approaches is sufficient to restore compensation. For instance, increasing cardiac efficiency in paroxysmal tachycardias or reducing cardiac load in circulatory failure due to infusions of blood or saline may be sufficient to restore compensation. But in the vast majority of instances, both methods must be used simultaneously. Indeed, it seems probable that either method indirectly uses the other. Increasing cardiac efficiency decreases cardiac load by diminishing venous pressure and decreasing cardiac load increases cardiac efficiency by increasing the pressure gradient in the coronary arteries because of the drop in venous pressure.

Refractory heart failure may be due to suboptimal use of either or both methods.

One cannot speak of refractoriness to one method without knowing that the other method has been optimally used. Suboptimal therapy may be due to too little or too much treatment. Verbal separation of each aspect of treatment is necessary but in practice, various combinations are used simultaneously.

Increasing Cardiac Efficiency

a) *Digitalis:* This is the most effective drug. In refractory heart failure, the dose of the drug should be reviewed because there is no single digitalization or single maintenance dose. Nor is there any rule of thumb to gauge adequate digitalization except by the dissipation of congestive heart failure. Withering's advice should be followed, namely the dose should be increased gradually until the first symptoms or signs of toxicity appear or until one is certain that increasing failure is being produced. There are two exceptions to this rule: 1) acute inflammatory and 2) acute necrotic lesions of the myocardium. In these two instances, one must be satisfied with the average maintenance and digitalization doses because of the increased irritability of the myocardium and the consequent potentiality of sudden death.

Over digitalization can likewise lead to refractory heart failure. In addition to the usual symptoms and signs, one should be suspicious of digitalis intoxication in an individual who is on a greater than average maintenance dose and is developing increasing congestive heart failure with no other apparent cause.

b) *Quinidine:* This drug is indicated in auricular fibrillation with a rapid ventricular rate not controlled by digitalis. It is also of value when there are multiple premature beats not caused by or abolished by digitalis if these beats distress the patient or if it is thought that they contribute to wasteful expenditure of much needed cardiac work. Electrocardiographic examinations should be made after three to five days of administration of the drug and before each increase in dosage. Recently, experimental evidence has been advanced that quinidine may increase the cardiac output of the diseased human heart. This evidence supports the clinical impression, that is difficult to document and that is contrary to accepted practice, that in a small percentage of instances, quinidine may act synergistically with digitalis to maintain compensation.

c) *Oxygen:* This is particularly indicated when there is interference with respiratory exchange of gas or when precordial pain is present. There are many methods of administering oxygen. The oxygen content within the tent cannot be determined by the gauges on the oxygen tank. The oxygen content of gas within the tent should be determined at frequent intervals.

d) *Vasodilators:* It is difficult to evaluate clinically the effects of vasodilating drugs. So long, however, as they do not produce undesirable symptoms, they should be used for whatever good effect they may have. Papaverine has an added sedative effect and aminophyllin, by suppository or intravenously, has the added effect of relieving dyspnea and of increasing the flow of urine.

Decreasing Cardiac Load

Rapid methods of decreasing cardiac load utilize 1) mechanical methods of removing blood and extravascular fluid collections, 2) the use of tourniquets on the four extremities to prevent excessive venous return of blood to the heart, and 3) the use of blood pressure lowering drugs such as tetraethylammonium bromide. Important as these methods are, they are obviously not suitable for chronic overloading for which the following is used:

a) *Rest:* This includes both physical and mental rest, bed rest if necessary, sedatives, laxatives, small easily digested meals, and treatment of all distressing symptoms.

b) *Water:* This is essential for the kidneys to excrete the load imposed upon them by the diet. The amount of water needed for a given load varies inversely with the concentrating power of the kidneys. Approximately 1.0 to 1.5 cc. of water for each calorie ingested is more than ample unless there is extensive renal disease or excessive extra renal loss of water. In congestive heart failure, the kidneys are malfunctioning as indicated by the presence of protein, red blood cells, and casts in the urine. The blood urea nitrogen is normal. The blood sodium and chloride are either low normal or slightly below normal. If the water intake is inadequate, more protein, casts, and red blood cells appear in the urine and the specific gravity rises to 1.025 or higher. Hypertonic dehydration of the blood appears characterized by a urea nitrogen rise to 40 mg. and a rise of the sodium and chloride to a high normal or even above normal. In the older individual with atherosclerotic kidneys, the blood urea nitrogen may rise above 100 mg. Uncorrected hypertonic dehydration produces refractory heart failure. This situation demands more water and other methods of promoting sodium diuresis. It is important that these findings should not be regarded as a contraindication to the use of mercurial diuretics.

If the water intake is increased without changing the sodium intake, the amount of

sodium of the diet offered to the kidney per unit of volume of water decreases so that ultimately endogenous sodium is excreted. The patient is given the amount of water estimated as needed and is then permitted as much more as his thirst dictates.

c) *Sodium restriction:* This method is much more effective in diminishing the sodium content of the diet offered to the kidney per unit volume of water. This regimen is limited by 1) renal disease which prevents conservation of base, 2) its unpalatability, and 3) its frequent inadequacy with respect to vitamins and proteins. Refractory heart failure may be due to the production of occult beri-beri or possible other vitamin deficiencies. This eventually can be prevented by the use of vitamin supplements. Refractory heart failure may also be produced by hypoproteinemia induced by the diet. Hypoproteinemia is enhanced by the loss of protein and liver dysfunction due to heart failure itself and also by mechanical removal of extra vascular fluid. Once significant hypoalbumenemia is permitted to occur, heart failure may remain refractory to all treatment including intravenous albumen, plasma, or blood. Every effort should be made, therefore, to keep the blood proteins at a high normal level because of the extreme difficulty of correcting the blood proteins once they have fallen below normal and the consequent almost complete refractoriness of the heart failure. To maintain a high normal blood protein, it may be necessary to use specially prepared salt free protein foods.

Hypotonic dehydration occurs rarely with either excessive water ingestion or sodium restriction but it occurs more commonly after the use of

d) *Mercurial diuretics:* These are the most powerful and rapid sodium eliminating drugs. They are contraindicated in acute inflammatory renal lesions. Refractory heart failure may be due to inadequate use of these drugs. They may be used daily so long as the kidneys respond adequately. Adequate response is regarded as a urinary output above 2500 cc. or a loss of two pounds or more. Occasionally the kidneys may not respond at first. The drug may be repeated provided there are no toxic or unavoidable and undesirable side effects. Toxic effects are recognized by a rapidly rising blood urea nitrogen not explainable on the basis of hypertonic dehydration rather than the expected fall. This event occurs when the drug is used in the presence of acute inflammatory nephritides or when the drug is used repeatedly in the face of diminishing response of the kidneys. Treatment consists in discontinuance of the drug. Rarely, Bal may be needed.

A rising Van den Bergh is another danger signal. Rarely, jaundice is clinically obvious. It is difficult to tell whether liver dysfunction is due to direct toxic action of the drug or due to the electrolytic imbalance which is invariably present. Allergic and other rare reactions have been attributed to these drugs.

Unavoidable Side Effects:

1) *Vitamin deficiencies:* The tendency for the salt poor diet to be poor in vitamins is enhanced by diuresis which may cause excessive loss of water soluble vitamins. Although this event has not actually been proved, it is well to supplement the diet with a polyvalent preparation and, if beriberi or pellagra is suspected, to use thiamin chloride or nicotinic acid parenterally. Liver extract is also used if liver damage is suspected because liver damage tends to retain water and to produce refractory heart failure.

2) *Hypocalcemia:* The blood calcium is rarely below normal but symptoms of carpopedal spasm occurring in the morning on arising are not too rare when mercurials are given at frequent intervals. Calcium lactate by mouth or calcium gluconate intravenously helps to relieve these symptoms. Digitalization has not been regarded as a contraindication to the use of calcium when these symptoms are present.

3) *Hypochloremic Alkalosis:* The mercurials produce a rapid drop in blood chloride without at first affecting the blood sodium. There is a corresponding rise in CO_2. When the chloride drops below 86 meq., the individual tends to become refractory to the drug. The blood chloride can be raised by a) *oral NH_4Cl:* The enteric coated capsule is poorly absorbed and it may take, not two or three days, but seven to ten days to raise the chloride to normal; b) *intravenous NH_4Cl:* This is rarely necessary. For the cardiac there is no safe dose or safe rate. No attempt is made to replace in one dose the estimated deficit. A 2% solution in amounts of 250 cc. is given slowly (not more than 5 cc. per minute) and careful physical and if needed, laboratory examinations are made before each succeeding dose; and c) *cation exchange resins:* These resins exchange their H^+ or NH_4^+ for cations of the diet to unite with Cl^- which is readily absorbed. There is an increase in blood chloride and a tendency to produce acidosis which counteracts the alkalosis present.

These resins have been introduced primarily for sodium depletion. Their advantage consists in permitting a higher sodium content of the diet which is therefore more palatable. They are contraindicated in renal

disease. Their usefulness is also limited by their inability to differentiate sodium from potassium, calcium, and magnesium.

4) *Hyponatremia:* This occurs more commonly in renal disease and when frequent injections of mercurials are combined with NH_4Cl and the administration of large quantities of water. This regimen produces hypotonic dehydration which if uncorrected, leads to vascular collapse, shock, and death. Again, no attempt is made to replace in one dose the estimated deficit of sodium. The sick cardiac cannot tolerate sudden changes in chemical equilibrium. Intravenous hypertonic (3-5%) saline is given in amounts of 250 cc. Careful physical and if necessary laboratory examinations are made before each succeeding does is given.

5) *Hypochloremic Acidosis:* This situation is a late manifestation and may be due to starvation, renal disease, or other factors. Attempts at chemical correction have not proved satisfactory. Diuretics are stopped and the patient is permitted to eat whatever foods he desires including salt. This regimen will produce increasing congestive heart failure but paradoxically the patient feels better. He may gain as much as 10 to 20 pounds and remains fairly comfortable except for worrying about his swollen legs. It should however be remembered that marked chemical derangements can kill quickly whereas mild and even moderate congestive heart failure can be stationary for weeks, months, or even for years. This is particularly true of the rheumatic and of the older hypertensive patient with predominant right heart failure. After two to three weeks of this regimen, the chemical derangements may correct themselves except for a high blood urea nitrogen which indicates hypertonic dehydration. The individual may then again respond to a low salt and mercurial regimen.

It is premature to evaluate the following measures suggested for refractory heart failure such as 1) operative procedures such as valvuloplasty, pulmonary vascular anastomoses, and ligation of the inferior vena cava, 2) the reintroduction of partial destruction of the function of the thyroid gland, this time by radio-active iodine, and 3) the use of substances derived from the pituitary and adrenal glands.

It is obvious that the battle against congestive heart failure will continue until the mechanisms of normal and abnormal myocardial contractions are understood. In the meantime, the patient must be treated as a whole. One must be alert to derangements produced by treatment itself. The chemist should be invited not only to study the living patient but also to help determine the chemical derangements that produced death. It is hardly of value to have the pathologist demonstrate in an individual who died of heart failure a stenotic mitral valve the presence of which was known to the clinician for many years before the onset of failure.

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